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Original article

Photodynamic therapy with verteporfin for polypoidal choroidal vasculopathy treatment: 3-year results in Taiwan

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ABSTRACT

Purpose: The purpose of this study was to investigate the treatment efficacy of photodynamic therapy (PDT) with verteporfin for patients suffered from polypoidal choroidal vasculopathy.
Methods: In this retrospective comparative study, we included 25 eyes of 25 patients with macula-involved polypoidal choroidal vasculopathy. All patients had follow-up of more than 3 years. We compared the best-corrected visual acuity (BCVA) in logarithm of minimal angle of resolution (logMAR) scale at each follow-up time points with initial baseline BCVA. We also investigated the factors influencing final BCVA at the 36-month follow-up time point.
Results: At 6 months, the mean BCVA improved from 0.77 to 0.68 ($p = 0.024$). All the mean BCVAs after the 6-month follow-up time points were still better than baseline mean BCVA, but the improvements were not significant statistically. The mean BCVAs became 0.68, 0.74, 0.75, 0.73, and 0.72 respectively at 12-month, 18-month, 24-month, 30-month, and 36-month follow-up time points. Better initial BCVA ($p = 0.012$) and smaller lesion size ($p = 0.031$) significantly predicted the better final visual improvement at 36 months rather than sex ($p = 0.7$) and age ($p = 0.206$).
Conclusion: Although the visual improvement after treatment of PDT with verteporfin was only temporarily significant, the prevention of visual deterioration in these patients persisted during a 3-year follow-up. Better initial BCVA and smaller lesion size were significant factors influencing final visual improvement, and early treatment might be suggested.

1. Introduction

Polypoidal choroidal vasculopathy (PCV) was first described by Yannuzzi and others[1] in 1990 and is characterized by peculiar choroidal vascular networks terminating in aneurysmal or polypoidal lesions.[2,3] These lesions often leak extensively and produce subretinal fluid (SRF), intraretinal fluid (IRF), and retinal pigment epithelium detachment (RPED).[4,5] In fundus examination, the polyps look like orange-red protruding nodules and may involve the macular, peripapillary, midperiphery, or nasal area.[2,6] The prevalence of this disease is relative high in the Asian population, especially the Japanese.[7–9]

The natural course of PCV is highly variable and depends on factors including location, lesion sizes, and associated bleeding. Occasionally, acute and severe loss of vision may happen to PCV patients due to massive submacular or vitreous hemorrhage from spontaneously ruptured vessels.[5,10] In a long-term natural course study, Uyama and others[5] found that 50% of patients had a favorable course and in the remaining 50% followed a long-term persistent course with progressive visual loss because of recurrent hemorrhage or exudation. Although several treatment strategies have been proposed, such as laser photocoagulation, photodynamic therapy (PDT) with verteporfin, selective photothrombosis, and intravitreal injection of anti-vascular endothelial growth factor (VEGF), there is still no consensus about the most effective treatment of PCV.[11–18]

PDT with verteporfin (Visudyne; Novartis Pharma AG, Basel, Switzerland) has shown good results for PCV. Several studies revealed improved or stable vision, but recurrent or newly developed lesion was not infrequent and the visual acuity would be affected during a longer follow-up.[13–15,19–21] Recently, bevacizumab, an anti-VEGF, has also been used to treat PCV and was

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found to be effective for reducing the subretinal fluid of PCV lesion. However, the choroidal lesion was unaffected by this treatment alone.[17,18,22] In this study, we reported our 3-year treatment results of PDT with verteporfin for PCV patients in Taiwan.

2. Methods

This retrospective analysis was approved by the Institutional Review Board of the National Taiwan University Hospital in Taipei, Taiwan. Patients with macula-involved PCV and treated with PDT with verteporfin from January 2007 to June 2011 were enrolled in our study. The diagnosis of PCV was made based on the finding of characteristic polyp-like hyperfluorescence with or without a branching vascular network on indocyanine green angiography (ICGA). The inclusion criteria were as follows: (a) juxtafoveal, subfoveal, or extrafoveal active macular polypoidal lesions on ICGA, (b) macula-involved active lesion, such as submacular fluid, recent hemorrhage, lipid exudates, and macular edema as evidenced by optical coherence tomography (OCT) or fluorescein angiography (FAG), (c) initial best-corrected visual acuity worse than 20/32 [0.2 logarithm of minimum angle of resolution (logMAR)], (d) greatest linear dimension of lesion $\leq$ 5400 μm, and (e) follow-up $>$ 36 months. The exclusion criteria were as follows: (a) other ocular disease, such as epiretinal membrane, intraocular inflammation or infection, diabetic retinopathy, (b) previous treatment for PCV, (c) any systemic contraindication to verteporfin or angiographic dyes, such as porphyria, (d) severe systemic disease, such as cerebral vascular accident, liver disease, and (e) scar tissue that accounted for more than one-half of the PCV lesion.

Best-corrected visual acuity (BCVA), tonometry, and funduscopy were performed before treatment and at each follow-up. OCT, FAG, and ICGA were performed before treatment and at the 3-month interval. Follow-up visits were arranged 1 week after treatment and monthly thereafter. The BCVA measurement used the Snellen chart and then was converted to logMAR values. The patients received one session of PDT at baseline. If leaking polyps were found on ICGA, additional sessions of PDT every 3 months would be performed until the disappearance of the leaking polyps.

PDT with verteporfin infusion and laser application were performed using the full-fluence dose according to the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy protocol.[23] The difference in BCVA values between baseline and 6-, 12-, 18-, 24-, 30-, and 36-month follow-up time points were analyzed using the Wilcoxon signed rank test. A increase in BCVA of more than three lines (logMAR BCVA change $\geq$ 3 lines) was considered improved and a decrease of more than three lines (logMAR scale) was considered aggravated. The percentage of BCVA improved and aggravates were also analyzed at 6, 12, 18, 24, 30, and 36 months. Furthermore, we used linear regression test to investigate if age, sex, lesion size, and baseline BCVA had a significant impact on final visual outcome at 3 years of follow-up. Paired *t*-test and linear regression were performed for statistical analysis. Initial BCVA, lesion size, sex, and age were included in linear regression for multivariate analysis. Statistical analysis was performed using SPSS 11.5.1 for Windows software package (SPSS Inc, Chicago, Illinois, USA). A $p < 0.05$ was considered significant.

3. Results

From January 2007 to June 2011, 25 eyes of 25 patients treated for PCV with verteporfin in National Taiwan University Hospital were included in our study according to the criteria described previously. The details of patient characteristics are listed in Table 1. The mean BCVA scores in logMAR scale over time are displayed in Fig. 1 and Table 2. The mean BCVA at baseline was 0.77 ± 0.39. The mean BCVAs at post-treatment at 6, 12, 18, 24, 30, and 36 months became 0.68 ± 0.43, 0.68 ± 0.47, 0.74 ± 0.47, 0.75 ± 0.50, 0.73 ± 0.48, and 0.72 ± 0.48 respectively. The improvement of BCVA was significant statistically 6 months after treatment ($p = 0.024$).

Table 1
Baseline characteristics and treatment outcomes of 25 eyes of 25 patients with polypoidal choroidal vasulopathy.

Gender	
Male, no. (%)	14 (56%)
Female, no. (%)	11 (44%)
Age (years)	
Mean ± SD	65.2 ± 10.1
Baseline greatest linear dimension of lesion (μm)	
Mean ± SD	2915 ± 1182
Baseline log MAR BCVA	
Mean ± SD	0.77 ± 0.39
RPED, no. (%)	19 (76%)
SRH, no. (%)	16 (64%)
Treatment times	3.16
Residual leakage on ICGA	1 (4%)
Residual RPED, SRF, IRF	4 (16%)

BCVA = best corrected visual acuity; IRF = intraretinal fluid; log MAR = logarithm of minimal angle of resolution; RPED = retinal pigment epithelial detachment; SRF = subretinal fluid; SRH = subretinal hemorrhage; SD = standard deviation.

As shown in Fig. 2, at the 6-month follow-up, 16% of the patients gained vision more than three lines and 8% of the patients lost vision more than three lines. At the 12-, 18-, and 24-month follow-up time points, 24%, 24%, and 28% of the patients gained vision of more than three lines, respectively; 16%, 16%, and 24% of the patients lost vision of more than three lines, respectively. At the 30- and 36-month follow-up time points, 24% and 24% of the patients gained vision more than three lines, respectively; 20% and 16% of the patients lost vision more than three lines, respectively.

During the 3 years follow-up, the patients received a mean of 3.16 treatments. At the 36-month follow-up time point, 4% patients had residual leakage on ICGA and 16% patients had lesions with residual RPED, SRF, or IRF (Table 1). Based on the results of

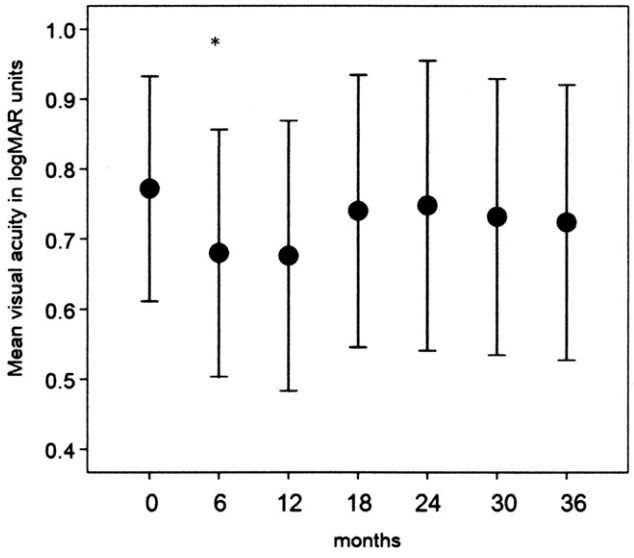

Fig. 1. This plot graph showing changes in mean best corrected visual acuity in logMAR units during the 36-month follow-up. The error bar values indicate the standard deviation. The improvement of BCVA was only significant statistically at 6 months follow-up time point (* indicate $p < 0.05$).

Table 2
Visual acuity during 36-month follow-up (data presented as mean ± SD).

Time from initial treatment (months)	Log MAR BCVA	P value (V.S. baseline)
0	0.77 ± 0.39	
6	0.68 ± 0.43	0.024
12	0.68 ± 0.47	0.085
18	0.74 ± 0.47	0.572
24	0.75 ± 0.50	0.715
30	0.73 ± 0.48	0.499
36	0.72 ± 0.48	0.428

BCVA = best corrected visual acuity; log MAR = logarithm of minimal angle of resolution; SD = standard deviation.

multivariate analysis, better initial BCVA ($p = 0.012$) and smaller lesion size ($p = 0.031$) significantly predicted the better final visual improvement at 36 months. Sex ($p = 0.7$) and age ($p = 0.206$) did not have the significant affect on the final BCVA change.

There was no complication such as infection, inflammation, or retinal detachment happened during follow-up in all of the patients. However, massive subretinal hemorrhage or breakthrough vitreous hemorrhage developed in four eyes (16%), RPE tear developed in three eyes (12%), and the BCVAs of these eyes all severely deteriorated. Massive subretinal hemorrhage or breakthrough vitreous hemorrhage happened in two eyes within 1 week after PDT treatment and may associate with the treatment. The other two eyes suffered from massive subretinal hemorrhage or breakthrough vitreous hemorrhage 2 months after PDT treatment and may not be associated with PDT treatment.

4. Discussion

PCV is one type of choroidal neovascularization but is different from age-related macular degeneration (AMD). Compared with AMD, PCV is thought to have better visual prognosis. However, once the lesion area extending to subfoveal area, visual prognosis will be poor.[7] In order to find out the best treatment modality, many studies investigated and compared the effect of PDT, intravitreal injection of anti-VEGF, or combination therapy. But, there was much disparity existed between these studies. Romano and coauthors[24] and Sato and others[25] showed significant visual acuity improvement after 1 year combined treatment of PDT and intravitreal injection of bevacizumab (IVB). Gomi and associates[26] also reported significantly better results of combined therapy compared with PDT monotherapy after 1 year of treatment. However, according to the study of Rouvas and others,[20] photodynamic therapy resulted in a significantly better outcome than ranibizumab or PDT with ranibizumab after 1 year of follow-up. Since the treatment results of PCV had much disparity and the case numbers of these studies were relatively small, we reported our 3-year results of PDT monotherapy for a better understanding of the treatment effect.

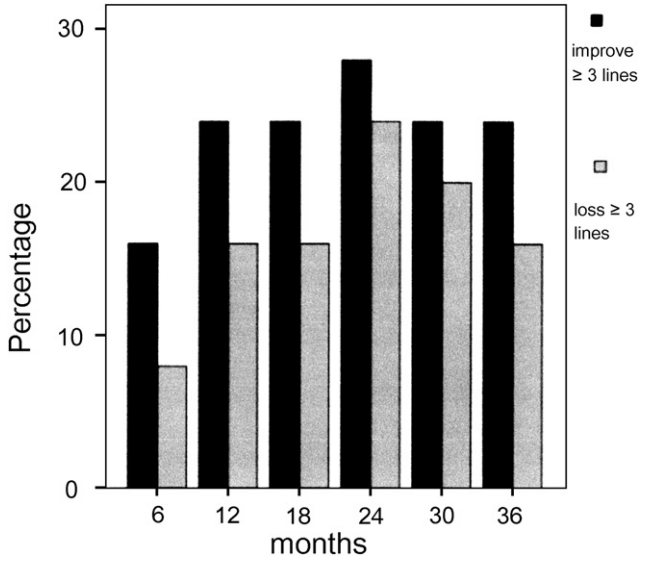

Fig. 2. The rates of eyes with a BCVA improvement of ≥3 lines or loss ≥3 lines at 6, 12, 18, 24, 30 and 36 months were showed in this graph.

Our results were similar to the reports of Akaza and colleauges[19] andLeal and coauthors[21] The visual acuity improvement was more apparent during the first year after treatment. However, the improvement became less significant with time. In our study, the mean BCVA changed at the 3-year follow-up time point and was an improvement of 0.07 in the logMAR scale. In the study by Akaza and colleagues,[19] a mean BCVA loss of 0.06 logMAR 3 years after PDT treatment was reported. In the study by Leal and others,[25] a mean BCVA loss of 0.02 logMAR was reported. All of these mean BCVA changes were not significant statistically.

According to several previous studies, vascular lesions could be controlled by PDT successfully, but the adverse events of RPE damage and scar formation would occur after treatment and result in persistent deterioration of visual acuity.[27–29] Since the RPE damage and scar formation is difficult to avoid, and better initial visual acuity results in the favorable visual outcome according to previous and our studies, early treatment for smaller lesion would be a good option to minimize the tissue damage and to obtain the better prognosis.[30] Furthermore, patients with subfoveal lesion usually had the worst initial BCVA and final BCVA compared with patients with extrafoveal lesions. Early treatment could also prevent further damage of retinal cells from polypoidal lesions itself.[5]

The limitations of this study include its small number of patients, retrospective study design and lack of macular thickness OCT measurement. Although the 3-year follow-up period is longer than most previous studies, it is not enough to clarify the long-term treatment outcomes and complications. On the other hand, converting Snellen BCVA to logMAR may cause some bias in the statistical analysis. Further studies with multicenter, double-blindness, and long-term follow-up are necessary to confirm the best protocol for PCV treatment.

In summary, our findings demonstrated that treatment of PDT with verteporfin for symptomatic PCV could temporarily improve mean BCVA and may prevent visual loss until three years follow-up. Our study also illustrated that initial visual acuity and lesion size were significant factors that influenced final visual improvement. Early treatment might be suggested after diagnosis of macula-involved PCV because patients with better initial visual acuity and smaller lesion sizes had more prominent visual improvement after PDT treatment.

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